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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,905	12/05/2006	**Shinya Yamanaka**	701049	9924

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EXAMINER
CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
07/08/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Chgpatent@leydig.com

Office Action Summary	Application No.	Applicant(s)	
	10/589,905	YAMANAKA, SHINYA	
	Examiner	Art Unit	
	Deborah Crouch	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16,22 and 71-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16, 22 and 71-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *August 18, 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed May 10, 2010 have been fully considered but they are not persuasive. The amendment has been entered. Claims 15, 16, 22 and 71-76 are pending.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 16 and 71-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method of screening for a candidate somatic cell nuclear reprogramming substance, which comprises the following steps:

(a) supplying ECAT4 to an *isolated fibroblast cell* comprising a drug resistance gene inserted into the ECAT4 gene such that the drug resistance gene is operably linked to the ECAT4 gene expression control region;

(b) contacting the supplied fibroblast cell with a test substance;

(c) determining the presence or absence of surviving fibroblast cells in a selection medium; and

(d) selecting a test substance that allows the emergence of surviving fibroblast cells as a candidate somatic cell nuclear reprogramming substance, and the screening method, wherein the fibroblast cell further comprises a marker gene operably linked to the expression control region of an ECAT gene selected from ECAT3, ECAT5, and Oct3/4;

does not reasonably provide enablement for methods of screening for nuclear reprogramming substance in vivo or isolated cells other than fibroblasts comprising a drug resistance gene inserted into an ECAT4 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The production of isolated cells for the presently claimed method requires the isolated cells undergo lengthy exposure to drugs for selection of the cells comprising the particular drug resistance gene inserted into the ECAT4 coding region. At the time of filing, it was known that for selection cells needed to undergo more than 45 divisions, a characteristic only recognized for ES cells, not a somatic cell as required, and fibroblasts, a somatic cell.

Thus the claims where the assay requires a cell having the disruption produced in vitro, the claims are limited to fibroblasts. Sedivy states when non-immortalized cells are targeted for insertional mutagenesis or "knock-out/knock-in" cells need sufficient proliferative capacity for 30-35 generations or doublings (Sedivy, page 89, col. 2, lines 2-6). Piedrahita states the cell preferred for possessing the ability to undergo the required number of passages without undergoing senescence are fetal fibroblasts (Pied page 45, col. 1, lines 4-12). Further, Williams shows primary epithelial cells were not suitable for the extensive culture needed for selection of a homologous recombination event (Williams, page 123, col. 1, lines 20-28). Williams points to senescence as preventing gene targeting events in somatic cells (Williams, page 123, col. 2, parag. 2, lines 1-6). Williams goes on to state all transgenic cloned large animals have been

produced from transfected fetal fibroblasts (Williams, page 123, col. 2, parag. 2, lines 13-15). Denning found that of primary somatic cells, fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer. (Denning, page 224, col. 2, lines 11-13 and page 224, col. 2, lines 16-19). Since the art found gene targeting events unpredictable in cells other than fibroblasts, the claims have been limited to fibroblast cells for the knockin event at the ECAT4 gene.

The present language of claims 15, 16 and 71-76 encompass somatic cells isolated from knock-in animals with a drug resistance gene inserted into both genes of ECAT4. If both ECAT4 genes, encoding Nanog, were absent, and functional ECAT4 not supplied, the animal embryos would not develop into live-born animals; no cells would be obtained (specification, page 47, lines 19-29). Thus, the claims are limited to isolated fibroblasts, which, for the reasons presented above, are the only cells capable of in vitro homologous recombination to produce multiple insertions into their genome.

With regard to knock-in animals, claim 22 represents the allowable scope, mouse. At the time of filing, only mouse ES cells, required to produce knock-in animals, were known in the art at the time of filing to colonize the germ line. Prelle state “there is no published data reporting live born, fertile germ line chimeras in mammalian species other than mouse” (page 222, col. 2, parag. 1, lines 14-16). Thus, for providing somatic cells, the claims would be enabled for mouse only, see below.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the screening method of claim 15, wherein the

source of the somatic cell is a mouse comprising a *heterozygous* insertion of a drug resistance gene into the ECAT4 gene such that the drug resistance gene is operably linked to the ECAT4 gene expression control region, does not reasonably provide enablement for t screening method of claim 15, wherein the source of the somatic cell is a knock-in mouse comprising a knock-in of a drug resistance gene into the ECAT4 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The present language of claim 22 encompasses mice with a drug resistance gene inserted into both genes of ECAT4. If both ECAT4 genes, encoding Nanog, were absent, and functional ECAT4 not supplied, the mouse embryos would not develop into live-born mice (specification, page 47, lines 19-29). Thus, the claim is limited to the mice being heterozygous for the insertion of a drug resistance gene into ECAT4.

For these reasons, the skilled artisan at the time of filing would have needed to perform an undue amount of experimentation without a predictable degree of success to implement the claims for their full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 15, there is confusion as to supplying ECAT4 to a cell and bringing the cell in contact with a test substance. The claim is not clear as to how one would discern an effect of supply ECAT4 from the effect of the test substance.

While applicant's explanation clarifies what is intended to be stated in claim 15, the claim as written is confusing. A suggested alternative is to review claim 15 as written in the scope rejection. The claim would be much clearer if the supplying of ECAT4 were separated from the contacting.

Claim 22 is confusing as to the operable linkage of the drug resistance gene. A suggested rewrite of claim 22 is:

The screening method of claim 15, wherein the source of the somatic cell is a knock-in mouse comprising an insertion of drug resistance gene into the ECAT4 gene such that the drug resistance gene is operably linked to the ECAT4 gene expression control region.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,

> except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 15, 16, 22 and 71-76 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by PgPub 20080280362. efd. November 26, 2003, now U.S. Patent 7682828 (Jaenisch).

Jaenisch teaching an in vitro assay for determining compounds that affect expression of pluripotency genes, such as Oct-4, Nanog (ECAT4) and Stella, where a transgenic cell comprising a selectable marker gene, such as an antibiotic resistance gene, operably linked to a pluripotency gene promoter is treated with an agent ([0027], [0035], [0058] and [0059]). Cells that express the marker gene are then selected as reprogrammed cells, thereby identifying or selecting the agent as a "reprogramming agent ([0058]). For example, when the marker gene is for antibiotic resistance, those cells that survive the antibiotic are deemed selected ([0029]). Jaenisch teaches the transgenic cell can be isolated from a heterozygous transgenic mouse whose genome comprises a single selectable marker knocked-in to a pluriopotency gene such that the marker gene is regulated by the pluripotency gene promoter ([0033]). Further Jaenisch teaches the assay may use cells containing additional marker genes operably linked to pluripotency protein promoters (claims 1-12). Thus, Jaenisch clearly anticipates the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (571)272-0727. The examiner can normally be reached on M-Fri, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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